

Anti-hypertensive treatment efficacy in patients with arterial hypertension and coronary artery disease or coronary equivalent

Ocena skuteczności leczenia hipotensyjnego pacjentów z nadciśnieniem tętniczym i chorobą niedokrwienną serca lub ekwiwalentem wieńcowym

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Abstract

Introduction. Arterial hypertension (AH) is a well-known cardiovascular risk factor. Currently, in Poland, approximately 32% of adults suffer from AH, and only 26% of them are treated successfully. The study aims to determine the incidence of atherosclerosis risk factors and their influence on the effectiveness of hypotensive treatment in the population of patients with AH and coexisting coronary artery disease (CAD) or coronary equivalent.

Material and methods. The study included 204 adults. The inclusion criteria were: diagnosis of AH with coexisting a diagnosis of CAD (138 people) or coronary equivalent defined as high ($\geq 5\%$) atherosclerosis-related risk of death in 10-year prognosis, estimated using the EURO SCORE scale (66 people). During observation, pharmacological and nonpharmacological treatments were modified according to the current AH treating standards. After 6 months of observation, the effectiveness of AH control was assessed.

Results. Multivariate logistic regression analysis revealed that main factors affecting poor blood pressure control after six months of observation were: obesity, age > 65 years, LDL cholesterol level > 130 mg/dL. Moreover, systolic blood pressure (SBP) < 140 mmHg was more frequent in patients with diabetes mellitus. After six months of therapy, good control of SBP was found in 42.7% of patients and normal values of diastolic blood pressure (DBP) — in 65.2 % of patients.

Conclusion. Independent risk factors for poor control of blood pressure were: high level of LDL-cholesterol, age > 65 years and female sex. Paradoxically, diabetes was not a risk factor for poor control of hypertension. The introduction of combined hypotensive and lipid-lowering drugs should contribute to a better control of hypertension in Poland.

key words: risk factors; arterial hypertension; treatment efficacy

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Streszczenie

Wstęp. Nadciśnienie tętnicze (AH) jest uznanym czynnikiem ryzyka schorzeń układu sercowo-naczyniowego. Obecnie 32% Polaków ma stwierdzone nadciśnienie tętnicze, z czego tylko 26% jest skutecznie leczonych. Celem pracy było określenie częstości występowania czynników ryzyka miażdżycy i ich wpływu na skuteczność leczenia hipotensyjnego w populacji pacjentów z AH i współistniejącą chorobą niedokrwienną serca (CAD) lub ekwiwalentem wieńcowym.

Materiał i metody. Kryterium włączenia do badania dla 204 osób stanowiło rozpoznanie HA (204 osoby), rozpoznanie CAD (138 osób) lub obecność ekwiwalentu wieńcowego rozumianego jako wysokie ($\geq 5\%$) ryzyko zgonu z powodu miażdżycy w ciągu najbliższych 10 lat, szacowane według skali oceny ryzyka SCORE (66 osób). W czasie obserwacji modyfikowano postępowanie niefarmakologiczne i farmakologiczne zgodnie z obowiązującymi standardami leczenia AH, ponownie oceniając uzyskaną skuteczność kontroli AH po 6 miesiącach.

Wyniki. Analiza wieloczynnikowa wykazała, że niezależnymi czynnikami wpływającymi na brak prawidłowej kontroli wartości ciśnienia tętniczego po 6 miesiącach były: otyłość, wiek > 65 lat, stężenie cholesterolu frakcji LDL > 130 mg/dl. Wykazano również, że pacjenci z cukrzycą łatwiej osiągnęli wartości skurczowego ciśnienia tętniczego (SBP) < 140 mm Hg. Po 6 miesiącach terapii zadowalającą kontrolę SBP odnotowano u 42,7%, a rozkurczowego ciśnienia tętniczego u 65,2% pacjentów.

Wnioski. Niezależnymi czynnikami ryzyka braku prawidłowej kontroli wartości ciśnienia tętniczego były: podwyższone stężenia cholesterolu frakcji LDL, otyłość, wiek > 65 lat i płeć żeńska. Paradoksalnie, cukrzyca nie była czynnikiem zwiększającym ryzyko nieprawidłowej kontroli wartości ciśnienia tętniczego. Wprowadzenie skojarzonych preparatów hipotensyjno-hipolipemizujących powinno w szczególny sposób przyczynić się do lepszej kontroli nadciśnienia tętniczego w Polsce.

słowa kluczowe: czynniki ryzyka, nadciśnienie tętnicze, skuteczność leczenia.

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Background

Arterial hypertension (AH) is a confirmed risk factor of cardiovascular diseases. Effective hypotensive therapy reduces morbidity and mortality associated with this disease [1].

Based on the results of NATPOL 2011 and POL-SENIOR trials, it was found that the number of adult Poles between 18 and 79 years old suffering from arterial hypertension was 9.8 million (32% of the overall population; 36.8% of the male population, 29.4% of the female population). This value reaches 34% when people over 80 years old are included (about 1 million people) [2, 3].

Due to increased awareness of the harmful effect of AH, the percentage of treated people is increasing systematically. Moreover, the number of patients who are aware of the presence of the disease is also increasing (change from 66% in 2002 to 72% in 2011). Unfortunately, 3.1 million people still do not know that they have AH, which may be due to the fact that 40% of Poles do not know their blood pressure values. Nevertheless, it seems beneficial that the proportion of successfully treated people increased from 12% (NATPOL PLUS 2002) to 26% in 2011 (NATPOL 2011) [2]. The prevalence of arterial hypertension in Poland is comparable to some European

countries (Czech Republic, Romania, Portugal) and 5–10% higher than in Turkey and Italy. In 2011 the prevalence of arterial hypertension in Poland was 4.5% higher than in the United States of America and the proportion of successfully treated patients was 2 times lower [2]. It may be related to more frequent use of modern pharmacotherapy, including combined hypotensive drugs in these countries.

Coronary artery disease, first of all including myocardial infarction, is the leading cause of cardiovascular death and the first cause of death in Europe among people under 75 years old and is responsible for 12.9% of total DALY (disability adjusted life-years) [4].

The aim of the study was to attempt to identify interactions and correlations between effective hypotensive therapy and cardiovascular risk factors in patients with coexisting arterial hypertension and coronary artery disease (or coronary equivalent) under the care of a specialist cardiologist.

Material and methods

The study cohort consisted of 204 consecutive adult patients with AH (mean age of the study population was 64.4 years) under the care of the Car-

Table I. Basic clinical parameters of the study group

Parameter	n = 204
Sex (female)	118 (58)
Abdominal obesity	186 (91)
Metabolic syndrome (according to IDF)	172 (84.5)
Abnormal weight	127 (62)
Obesity	48 (23.5)
Dyslipidaemia	112 (55) to 88 (43)
Diabetes mellitus	68 (33.5)
Impaired carbohydrate metabolism	118 (58)
Chronic kidney disease GFR <90 mL/min	128 (62.5)

Data are presented as number (percentage) of examined patients. GFR — glomerular filtration rate; IDF — International Diabetes Federation

diologic Outpatients' Ambulatory Clinic in Gorzów Wielkopolski in the first decade of 21st century. Inclusion criteria were: 1) diagnosis of AH, coexisting with: 2) diagnosis of coronary artery disease (CAD) (138 patients); and/or 3) the presence of coronary equivalent, defined as high ($\geq 5\%$) risk of death from atherosclerosis in the next 10 years, estimated according to the EURO SCORE scale (66 patients). The primary clinical parameters for the study group are listed in Table I. Depending on the value of systolic blood pressure (SBP) and diastolic blood pressure (DBP) the patients were assigned to different subgroups of AH control, i.e. subgroups with normal (< 140 mmHg for SBP and/or < 90 mmHg for DBP) and abnormal blood pressure control (≥ 140 mmHg for SBP and/or ≥ 90 mmHg for DBP). During observation, non-pharmacological and pharmacological managements were modified according to the current guidelines for arterial hypertension diagnosis and management, increasing drug doses and implementing further hypotensive drugs. The efficacy of AH control was evaluated after 6-month therapy.

Data on age, sex, body mass index (BMI), cigarette smoking and the presence of diabetes mellitus were analysed. Among the results of laboratory tests, serum levels of triglycerides, total cholesterol, HDL-C, LDL-C and creatinine clearance were analysed. The data on coronary artery disease were also analysed: the previous diagnosis of coronary artery disease and pharmacotherapy.

Statistical analysis

The effect of selected factors on the analysed endpoint — effectiveness of blood pressure control — was investigated using a multivariate logistic regression model [5]. The analysis was performed by the

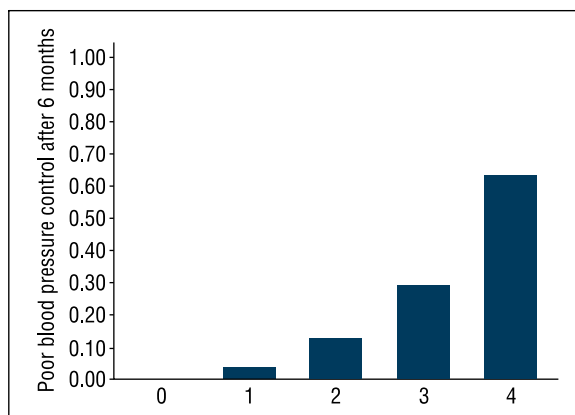


Figure 1. Risk of inappropriate systolic blood pressure control (after 6 month of treatment) depending on number of risk factors for poor control of blood pressure values (n = 33). **Interpretation of the graph.** Independent risk factors for poor control of blood pressure values were: obesity, age >65 years, high level of LDL cholesterol and absence of diabetes. The graph presents the relative risk of inappropriate systolic blood pressure control depending on the prevalence of: 0, 1, 2, 3 and 4 variables evaluated in the model presented in Table III. The highest risk of poor antihypertensive control was observed in patients aged > 65 years, with LDL-C > 130 mg/dL, without diabetes (bar 4). BMI — Body Mass Index; LDL-C — LDL cholesterol; N — number of patients; SBP — systolic blood pressure

stepwise elimination method, assuming the level of 0.1 to remain in the model and setting a threshold for statistically significant differences at 5%.

The predictive value of the final model was assessed with the use of ROC curves (so-called C statistics). Model's goodness of fit was checked by Pearson or Hosmer-Lemeshow tests. Good fit of the prognostic model for complications is a lack of statistical significance in the Pearson or Hosmer-Lemeshow tests. Statistical calculations were performed using licensed SAS and Excel programs.

Results

LDL-C elevation > 130 mg/dL, obesity, age > 65 years and female sex were found as important predictors for the risk of ineffective hypotensive therapy in the set of analysed features at the time point „after 6-month therapy”. Paradoxically, diabetes mellitus was not a factor that increased the risk of poor control of blood pressure (Figure 1, Table II).

After 6 months of treatment, 42.7% of patients were in the normal (< 140 mmHg) SBP group. The number of people with normal (< 90 mmHg) DBP values was significantly higher, accounting for 65.2% of the study population.

Table II. Risk of poor control of systolic blood pressure value — assessment after 6-month therapy

N = 33	OR (95% CI)	P
Age > 65 years	2.88 (1.18–7.02)	0.020
Male sex		> 0.1
Weight > 81 kg		> 0.1
Overweight (BMI 25–29.9 kg/m ²)		> 0.1
Obesity (BMI ≥ 30 kg/m ²)	7.13 (2.68–19.00)	< 0.001
Smoking		> 0.1
Diabetes mellitus	0.34 (0.13–0.91)	0.033
Coronary artery disease (CAD)		> 0.1
Triglycerides > 150 mg/dL		> 0.1
Cholesterol > 200 mg/dL		> 0.1
LDL-C > 130 mg/dL	2.66 (1.13–6.23)	0.024
HDL-C < 40 mg/dL		> 0.1
Creatinine clearance		> 0.1
Acetylsalicylic acid > 75 mg/day		> 0.1

BMI — Body Mass Index; N — number of patients; OR — odds ratio; p — level of statistical significance; 95% CI — 95-confidence interval

Table III. The odds ratio of the risk of poor blood pressure control for: systolic blood pressure (SBP), diastolic blood pressure (DBP), SBP and/or DBP, SBP and DBP

Parameter	SBP	DBP	SBP and/or DBP	SBP and DBP
Age > 65 years	2.88		2.05	
BMI ≥ 30 kg/m ²	7.13			16.54
Diabetes mellitus	0.34	0.19	0.29	0.14
LDL-C > 130 mg/dL	2.66	6.77	5.96	12.84
Male sex		0.26	0.29	
BMI 25–29.9 kg/m ²		0.07		
Weight > 81 kg			5.96	

BMI — Body Mass Index; DBP — diastolic blood pressure; SBP — systolic blood pressure

Discussion

From the analysis of the data in Table III, it can be concluded that only two factors have been predictors of insufficient blood pressure control after 6 months of treatment in all 4 models. These were: absence of diabetes and baseline LDL cholesterol level > 130 mg/dL. The baseline LDL-C abnormalities are associated with worse prognosis as to the effectiveness of the implemented and intensified therapy during 6 months of hypotensive therapy. The presence of diabetes, as noted in this study, paradoxically was associated with better antihypertensive control after 6 months of therapy. This may suggest that patients with diabetes, CAD and AH are treated more aggressively and more opti-

mally so they are more likely to achieve normal blood pressure values. According to the current guidelines of the Polish Society of Hypertension, the presence of diabetes is an indication for the implementation of a statin and hypotensive therapy in any case of hypertension [1].

Recent studies showed that patients with prediabetes may benefit from the combination of a statin and antihypertensive therapy. Chinese researchers (Huang et al.) have analysed the efficacy of atorvastatin and amlodipine combination in patients with prediabetes.

Forty-five consecutive patients with hypertension were divided into two groups based on the presence (HD group, *n* D 23) or absence (H group, *n* D 22) of prediabetes. All patients underwent 12-week treatment with daily single-pill amlodipine/atorvastatin combination. This treatment significantly reduced (*p* < 0.01) BP and blood lipid levels in H and HD groups to a statistically similar extent (*p* > 0.05). In the HD and H groups there were significantly (all *p*-values < 0.01) lower levels of markers of inflammation (ICAM-1 and TNF- α) with more pronounced reductions in patients with prediabetes. ICAM-1 level significantly (*p* < 0.01) decreased by 14.44% in the H group (from 3.81 ± 0.60 pg/mL to 3.26 ± 0.32 pg/mL) and by 24.82% in the HD group (from 4.07 ± 0.70 pg/mL to 3.06 ± 0.34 pg/mL). TNF- α level also significantly (*p* < 0.01) decreased after treatment by 20.47% in the H group (from 101.79 ± 11.72 pg/mL to 80.95 ± 9.33 pg/mL) and by 29.05% in the HD group (from 110.94 ± 10.71 pg/mL to 78.71 ± 9.19 pg/mL) [6].

Beta-blockers and ACE-inhibitors are recommended in patients with coronary artery disease and in cases of angina — calcium channel blockers (CCBs) are preferred [1]. Equally important is statin therapy in this group of patients.

Numerous publications report the pleiotropic effect of statins, such as improvement of endothelial function, enhancing the stability of atherosclerotic plaques, decreasing oxidative stress and inflammation, inhibiting vasoconstriction, stimulating and upregulating endothelial NO synthase (eNOS) [7]. Statins can reduce the hardening of the arteries, improve arterial compliance, improve left ventricular hypertrophy and inhibit cell proliferation by reducing angiotensin I [8].

Several lines of research indicate that statins can lower blood pressure (BP) independently of their lipid-lowering effects when used as monotherapy and in combination with antihypertensive agents. The PERSPECTIVA study performed in 2017 recruited 587 adults with untreated or uncontrolled hypertension and hypercholesterolaemia. All patients received

treatment with single-pill combination perindopril/amlodipine. Additionally, 226 patients in this group received the statin. During the 60-day follow-up, a better control of blood pressure was observed in statin [+] group (73% vs. 64%, $p < 0.05$) [9].

It has also been proven that combined treatment with a statin and a calcium channel blocker are more effective in reducing cardiovascular risk than each of these drugs used alone. This is due to the fact that these drugs have not only lipid-lowering and antihypertensive properties but also could increase the level of tissue plasminogen activator, increase compliance of small artery walls, and decrease insulin resistance [10].

Equally interesting are the findings from the European ALL-IN-ONE study. A total of 305 hypertensive patients were randomised 1:1. The “fixed group” (154 of patients) was given a once-daily fixed combination (ODFC) of perindopril 10 mg plus indapamide 2.5 mg plus amlodipine 5 or 10 mg plus atorvastatin 20 mg. The “free group” was given a free-drug combination (FDC) of the three antihypertensive agents plus atorvastatin 20 mg at the free time in the day. At 12-weeks, the fixed group had lower systolic BP (124.46 ± 6.4 vs. 129.02 ± 5.03 mmHg, $p = 0.002$) and similar diastolic BP (81.24 ± 3.4 vs. 83.09 ± 3.1 mmHg, $p = 0.082$) compared to the free group. BP targets at week 12 were more commonly reached with fixed than free combination (89% and 80% respectively, $p = 0.048$). For CV risk in both groups there was a significant reduction; however, CV risk reduction was greater in those taking ODF combination (fixed group — 38.5%; free group — 35.4%). Compliance was significantly greater in the fixed group vs. the free group (94% vs. 85% respectively, $p = 0.034$). There were no statistically significant differences between diastolic blood pressure, LDL-C level and adverse events [11].

A meta-analysis conducted by Bertrand *et al.* in August 2014 showed that administration of a combination of two antihypertensive agents and lipid-lowering therapy, such as an ACE inhibitor, a CCB, and a statin, in a single-pill formulation reduced the risk of myocardial infarction, sudden cardiac death and cardiovascular death by 46%. Furthermore, single-pill formulations (“polypill”) are known to result in better adherence to the treatment [12, 13].

Study limitation

Presented study was conducted in the first decade of the 21st century in Gorzów Wielkopolski. Based on the results of this study, the doctoral dissertation was created, graduated in 2007 at Medical University of Warsaw [14]. It has been decided now to report its

results after a decade due to the special validity of its conclusions.

Independent factors of poor hypotensive control were elevated LDL-C levels, which suggests the possibility of addressing this therapeutic problem using combined hypotensive-hypolipaeic drugs (atorvastatin + amlodipine; rosuvastatin + amlodipine; rosuvastatin + valsartan) or special triple drug combination (atorvastatin + perindopril + amlodipine) currently available and newly introduced onto the Polish pharmaceutical market. Conclusions of presented study are interesting after a decade in the context of too rare use of these drugs in nowadays clinical practice in our country [15, 16].

Conclusions

1. Independent risk factors of poor hypotensive control were: elevated LDL-C levels, obesity, age > 65 years and female sex. Paradoxically, diabetes mellitus was not a factor increasing a risk of poor hypotensive control.
2. In the study population diagnosis of coronary artery disease and kidney function impairment was not associated with a worse effect of hypotensive treatment.
3. Newly introduced combined hypotensive and lipid-lowering drugs should contribute to better control of arterial hypertension in Poland.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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